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Probable Opitz Trigonocephaly C Syndrome With Medulloblastoma

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We report on a patient with trigonocephaly, biparietal widening as a result of metopic synostosis, strabismus, upslanted palpebral fissures, apparently low-set ears with abnormal helices, deeply furrowed palate, postaxial polysyndactyly of the feet, ankle flexion deformities, cryptorchidism, loose skin, and severe mental retardation, findings compatible with a diagnosis of the Opitz trigonocephaly C syndrome (OTS). At the age of 12 years this patient presented with symptoms of raised intracranial pressure. A biopsy showed findings diagnostic of a medulloblastoma WHO Grade IV, an unprecedented finding in OTS. The possibility of coincidence should not prevent continued surveillance of OTS patients in the future for the occurrence of malignancy. Am. J. Med. Genet. 69:395–399, 1997.

KEY WORDS: **Opitz trigonocephaly C syndrome; medulloblastoma; dysmorphology; genetics**

INTRODUCTION

In 1969 Opitz et al. described a malformation syndrome in 2 sibs with trigonocephaly, which the authors called "The C syndrome of multiple congenital anomalies" [Opitz et al., 1969]. Additional findings were multiple labiogingival frenula, thick alveolar ridges and highly arched palate, epicanthal folds, strabismus, broad saddle-shaped nose, ear anomalies, hexadactyly, skin laxity and visceral anomalies. Subsequently, more than 20 cases have been reported with a similar phenotype and absence of chromosome aberrations by light microscopy. Cause is assumed to be an autosomal recessive mutation. Some of the reported cases had additional abnormalities such as pseudohypoaldosteronism [De Koster et al., 1990]. We here present the first case report of OTS with medulloblastoma.

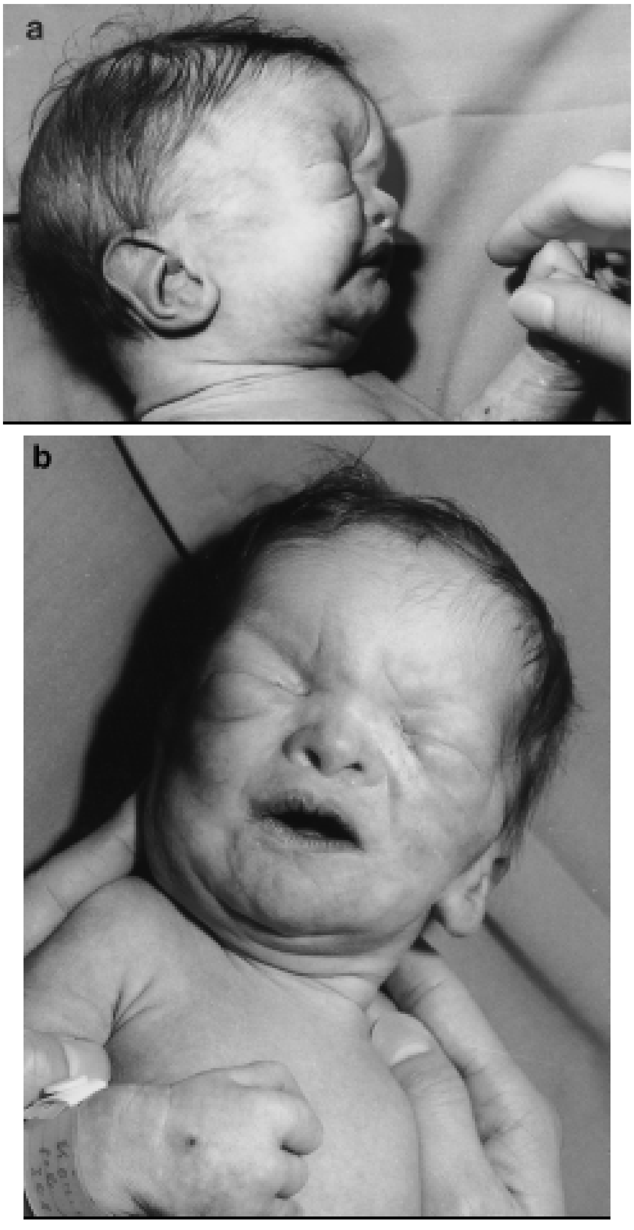

Fig. 1. **a, b:** Patient at the first day of life. Note the prominent forehead.

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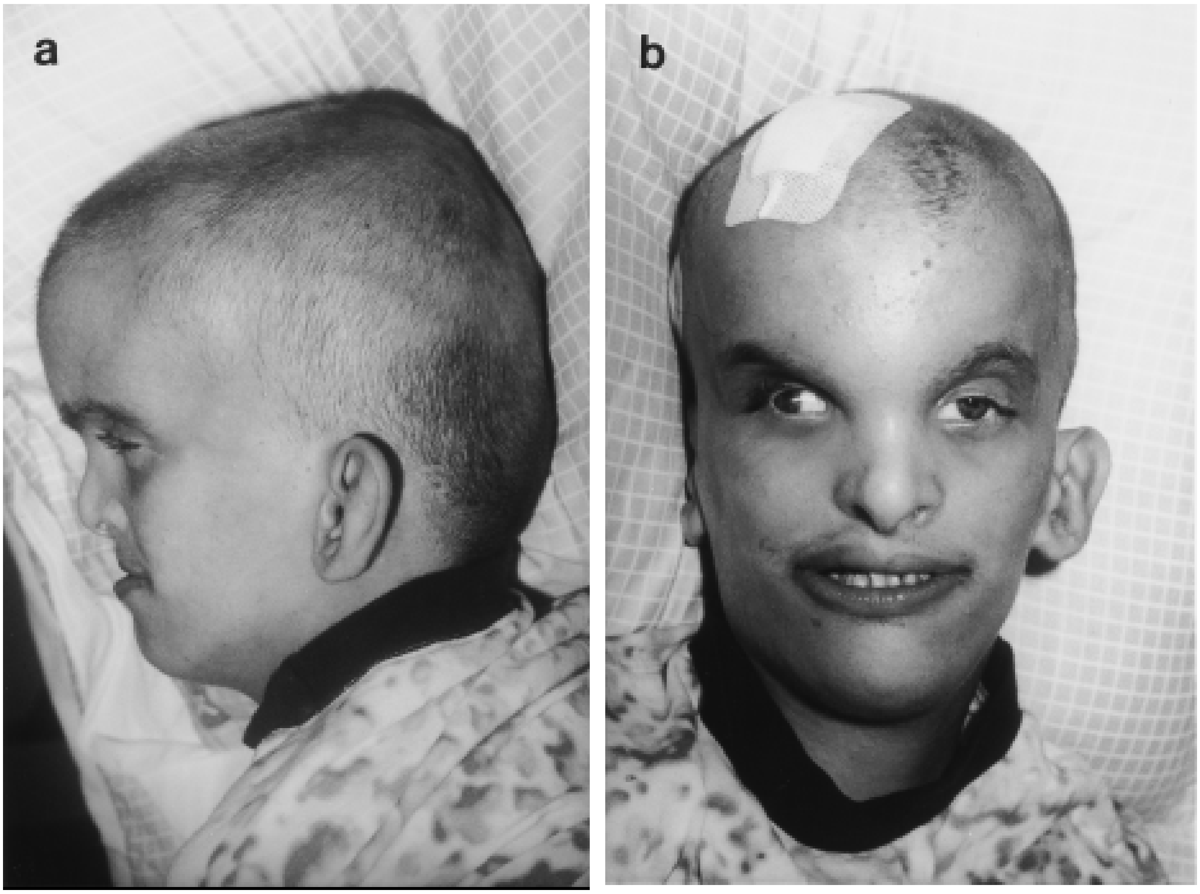

Fig. 2. **a, b:** Patient at age 12 years. Note the prominent forehead, posteriorly angulated auricles, strabismus and broad nasal bridge.

CASE REPORT

The patient was the first child of non-consanguineous German parents. Both parents were 21 years old. He was born at 40 weeks of gestation after an uneventful pregnancy by spontaneous vaginal delivery with a birth weight of 3,080 g and a length of 52 cm. Both parents were healthy with a noncontributory family history; 4 years later the mother gave birth to a healthy daughter.

At birth the infant was noted to have trigonocephaly with biparietal widening at the posterior aspect of the parietal bones (Figs. 1, 2). Other abnormalities included sparse scalp hair, apparently low-set ears with abnormal helices, upslanted palpebral fissures, epicanthal folds, broad nasal root, a deeply furrowed palate, broad alveolar ridges (Fig. 3), strabismus, bilateral atrophy of the iris, loose skin and hypoplastic scrotum with inguinal testes. Both feet showed postaxial hexadactyly, on the right with an additional proximal phalangeal bone, on the left without bony element. Flexion deformities were present at both ankles (Fig. 4). The infant had congenital hypotonia.

Sonography of the abdomen showed normal liver, spleen, kidneys and bladder. At 7 months right bundle branch block and subaortic stenosis were diagnosed but subsequently resolved.

The patient's neurologic development was complicated by the appearance of infantile spasms at 12 months with EEG findings of hypsarrythmia. Seizure activity was controlled by valproate and phenobarbital. His motor development was severely retarded. Head control began at age 2 years. He was able to bond to his parents. At 12 years he lived in partial residential care and it was reported that he was able to move by means of bottom shuffling. He vocalized but had no speech development.

At this age he presented acutely ill with lethargy, nausea and vomiting. An MRI examination of the head demonstrated a mass in the posterior fossa with obstructive hydrocephalus (Fig. 5) and increased intracranial pressure, which required ventriculo-peritoneal shunting. Histological examination of an open brain biopsy specimen demonstrated findings of a medulloblastoma WHO IV. Chromosomes of peripheral lymphocytes with an average of 650 bands per haplotype were apparently normal. Chromosome examination of the tumor tissue was not performed. The patient susequently died.

DISCUSSION

We report on a child with OTS. Until now 30 cases of presumed OTS have been reported [Opitz et al., 1969; Oberklaid et al., 1975; Preus et al., 1975; Antley et al., 1981; Flatz et al., 1984; Fryns et al., 1985; Sargent et

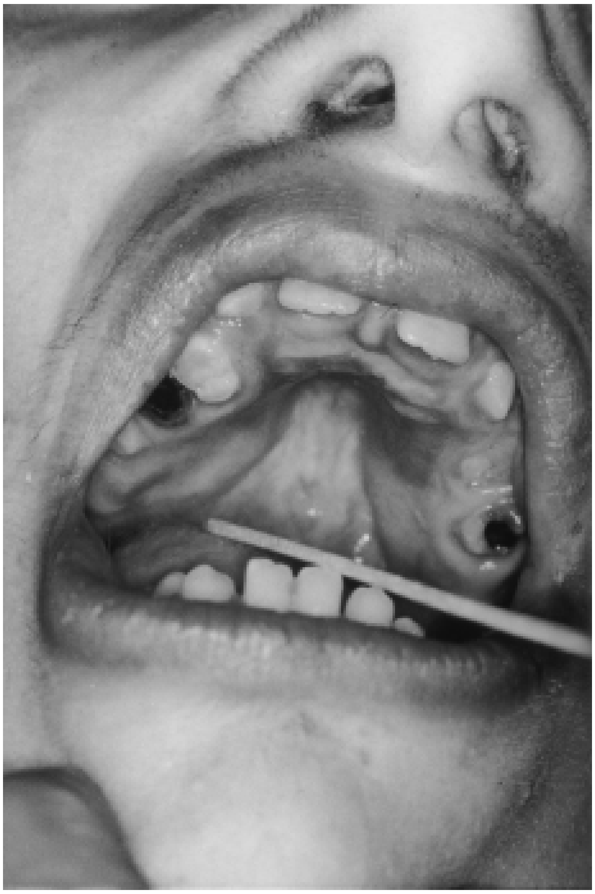

Fig. 3. Broad alveolar ridge and deeply furrowed palate.

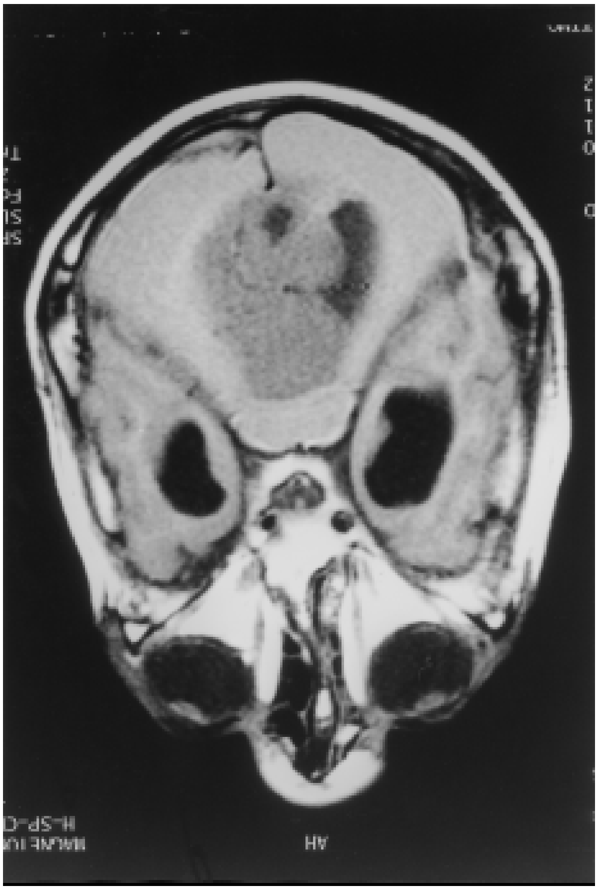

Fig. 5. Cranial MRI. Note the mass in the posterior cranial fossa and the obstructive hydrocephalus.

al., 1985; Preus et al., 1986; Camera et al., 1990; De Koster et al., 1990; Lalatta et al., 1990; Stratton et al., 1990; Haaf et al., 1991; Schaap et al., 1992; Chouduri et al., 1992]. On repeated chromosome analysis in 2 of these cases a duplication deficiency of chromosome 3 was detected [Sargent et al., 1985; Preus et al., 1986]. Schaap et al. [1992] reviewed the literature and described common and less common manifestations of 23 patients with OTS. Patients with detectable microdeletions, gross internal anomalies [Antley et al., 1981; Opitz et al., 1969], absent trigonocephaly [Preus et al., 1975] and normal mental development [Stratton et al., 1990] were excluded. We compared our data to the data of Schaap et al., [1992] and to those of Chouduri et al. [1992] (Table I). There are some striking common clinical findings, e.g. specific intraoral anomalies such as multiple labiogingival frenula, highly arched palate and broad alveolar ridges, that some authors consider diagnostic of OTS [Oberklaid et al., 1975]. However there is evidence for clinical variability in OTS. For example, a wide range of cardiac anomalies such as mitral stenosis [Sargent et al., 1985], complete atrioventricular canal [Antley et al., 1981], ventricular septal defect [Antley et al., 1981; Haaf et al., 1991; Chouduri et al., 1992], tetralogy of Fallot [De Koster et al., 1990] and persistent ductus arteriosus [Opitz et al., 1969; Haaf et al., 1990] were reported. Neurologic deficits comprised almost invariably mental retardation and hypotonia. Imaging of the CNS in most cases yielded normal results, but others showed "poor myelinization" [Opitz et al., 1969], cerebral atrophy, polymicrogyria, absent corpus callosum, ollivary dysplasia, cerebellar heterotopia and paucity of central white matter and descending tracts [Sargent et al., 1985], Dandy Walker malformation [De Koster et al., 1990] and spina bifida occulta [Schaap et al., 1992].

Because of normal karyotype, parental consanguinity and normal parents with multiple affected offspring

Fig. 4. Postaxial polydactyly and contraction deformity at 12 years.

TABLE I. Clinical Manifestations of OTS Summarised by Schaap et al. (1992) (23 Patients) and Data of a Single Case Report [Chouduri et al., 1992] in Comparison With the Presented Patient

Manifestations	Present case	OTS (n = 24)
Consanguinity	–	3/24
Sex	Male	12M/12F
Survival	12 years	Death before 2 years (5/24)
Cranium		
Trigonocephaly; metopic synostosis	+	24/24
Premature closure of other sutures	–	7/21
Microcephaly	+	15/22
Sparse scalp hair	+	6/21
Face		
Abnormally modelled low-set ears	+	23/23
Upslanted palpebral fissures	+	24/25
Epicanthal folds	+	22/24
Hypotelorism	+	5/19
Broad depressed nasal bridge	+	17/23
Anteverted nostrils	+	14/24
Long philtrum; small nose	–	22/25
Thin upper vermillion border	–	8/17
Oral cavity		
Micrognathia	–	16/24
Highly arched palate	+	17/22
Broad alveolar ridges	+	11/19
Attached frenula	–	7/22
Skeletal		
Short neck	–	15/22
Skin		
Loose redundant skin	+	15/21
Haemangiomas	–	9/19
Deep sacral dimple	–	6/19
Upper limbs (general)		
Postaxial polydactyly	–	3/23
Cutaneous syndactyly	–	1/23
Simian crease	–	10/24
Ulnar deviated fingers	–	4/24
Brachydactyly	–	3/24
Clinodactyly	–	7/24
Rhizomelic shortness	–	3/24
Lower limbs (general)		
Polydactyly	+	1/22
Syndactyly	–	3/23
Contractures; arthrogryposis	+	7/22
Hip dysplasia	–	6/23
Dislocated knees	–	4/23
Genitourinary		
Cryptorchidism	+	7/9
Heart		
Heart defect; cardiac murmur	+	12/23
Neurology		
Neonatal hypotonia	+	13/20
Seizures	+	5/20
Mental retardation (severe)	+	19/20

of equal sex ratio, autosomal recessive inheritance was suspected for OTS by some authors. However consanguinity was only found in 3 of 25 cases [Antley et al., 1981; Sargent et al., 1985; Haaf et al., 1991]. De Koster et al. [1990] proposed the possibility that OTS might be caused by a cytogenetically undetectable microdeletion syndrome. This view is supported by the number of trigonocephaly syndromes in which chromosome abnormalities have been reported including del(3p) (p12 $\rightarrow$ p14) [Schwyzer et al., 1987], dup(3q) (pter $\rightarrow$ q27) [Sargent et al., 1985], dup and del(3q) [Preus et al., 1986], del(7p) [Antley et al., 1981], del(9p) [Huret et al., 1988], del(11q) [Cassidy et al., 1977], del(13q) [Grace et al., 1971], dup(3q) [Hornstein et al., 1981] and partial trisomy and tetrasomy 13 [Chu et al., 1994]. Taking into account the clinical variability of OTS and the phenotypic resemblance of known aneuploidy syndromes genetic heterogeneity should also be considered in the OTS.

This is the first description of a medulloblastoma in a patient with OTS. "Primitive" neuroectodermal tumors of the central nervous system are the most common malignant brain tumors in children. Cytogenetic analysis of these tumors demonstrates frequent chromosome abnormalities. In particular deletions of 17p, 6q, 16q and 9q were detected [Thomas et al., 1991; McDonald et al., 1994; Schofield et al., 1995]. Other abnormalities included isochromosomy 17q, monosomy

17 and monosomy 22 [Vagner-Capodano et al., 1994]. The loss of genetic material from specific chromosome locations in a given tumor type has been taken as evidence of the importance of tumor suppressor genes at these loci in the genesis of the tumor. There is no overlap of known chromosomal abnormalities in OTS and medulloblastoma. We have no proof, but it is possible that a microdeletion may cause OTS and that the loss of the only functioning allele of a tumor suppresso r gene would result in the development of a medulloblastoma.

The risk for cerebellar medulloblastoma is known to be increased in basal cell nevus syndrome (9q31) [Gailani et al., 1992], Turcot syndrome and familial adenomatous polyposis (APC gene, 5q21–q22) [Hamilton et al., 1995]. Occasionally medulloblastoma was observed in the Li-Fraumeni syndrome, a cancer family syndrome [Pearson et al., 1982], which is probably caused by p53 gene mutations [Frebourg et al., 1995], Ataxia-Teleangiectasia syndrome (11q) [Gatti et al., 1991; Sobel et al., 1992] and Greig Cephalopolysyndactyly syndrome (GCS), which is most likely caused by a mutation in the GL13 gene (7p13) [Tommerup and Nielson, 1983; Hui and Joyner, 1993]. Only GCS shows a phenotype including syndactyly, polysyndactyly and expanded cranial vault, that partially resembles OTS. However mental retardation is in contrast to OTS not a feature of GCS. Preaxial polydactyly and bifid thumbs, which are noted in GCS are also no findings of OTS. Nevertheless because GCS and some cases of trigonocephaly syndromes are caused by del(7p) this locus might be a candidate for OTS.

The possibility of coincidence of OTS and medulloblastoma in this case does not obviate the need for tumor surveillance in the OTS.

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